## DETAILED ACTION

*Status of claims*

Claims 1, 6-7, 37 and 57-59 are pending.

The amendment filed 12/28/09 which amends claims 1 and 7, and cancels claims 2-5, 8-19 and 60-61 has been entered. Claims 8-19 were canceled by the amendment filed 4/13/09 and claims 20-36 and 38-56 were cancelled by the amendment filed 2/13/06. Claims 37 and 57-59 remain withdrawn from further consideration. Claims 1, 6 and 7 are under examination.

The sequences of SEQ ID NOs:1-14 have not been entered into USPTO Automated Biotech Sequence Search System databases because of error description of these sequences (see the attached report thereof).

***New-Objection to claims***

Claims 1, 6 and 7 are objected to becasue in claim 1, the term "protein" after "Zinc-finger antiviral protein (ZAP)" should be deleted.

***Withdrawal of objection and rejections***

[1] The objection of claim 7 is withdrawn in light of the amendment of claim 7.

[2] The objection to the specification is withdrawn in light of the amendment of the specification thereof.

[3] The 112/1 rejection of claims 1-4, 6 and 7 is withdrawn in light of the amendment of claim 1, and cancellation of claims 2-4. Yet, new rejection under 35 USC 112, first paragraph is applicable to the amendment of claim 1 and dependent claims therefrom (see below).

[4] The 103(a) rejection of claims 1 and 3-5 is withdrawn in light of applicants' submission of the declaration under 37 CFR 1.132 which overcomes the rejection, and in light of cancellation of claims 3-5.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[1] *Written description*

Claims 1, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The factors considered in the Written Description requirement are (1) Actual reduction to practice; (2) Disclosure of drawings or structural chemical formulas; (3) Sufficient relevant identifying characteristics; (4) Method of making the claimed invention; (5) Level of skill and knowledge in the art; and (6) Predictability in the art. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP § 2163.

Actual reduction to practice/Disclosure of drawings or structural chemical formulas.

The amended claim 1 and dependent claims 6, and 7 as written are directed to an isolated mammalian zinc-finger antiviral protein (ZAP) comprising 4 CCCH zinc finger motifs. Due to

the open-ended language "comprising" the protein having 5 or more CCCH zinc finger motifs also reads on instant claim 1.

The specification sets forth that the ZAP may bind to specific cellular RNAs and stabilize thereof (page 28, lines 19-23) and specific for the virus such as Nile virus (page 15, lines 16-123). Contrary to this, the art (US 20020035246 A1) teaches that CCCH zinc finger protein SMAD binds single or double stranded DNA (claim 22), suggesting not all the CCCH-type zinc finger proteins specifically bind RNAs only. The specification does not describe what structure renders the "specificity" thereof, nor provide factual indicia regarding the CCCH zinc finger motifs and/or the sequence(s) outside the motifs responsible for said specific viral binding function. The relative art does not teach in this regard either.

The relative art (US 20020035246 A1) teaches that the CCCH-zinc finger proteins such as 'SMAD interacting protein" (see [0039]) has an RNase activity (see [0043]) which degrade RNA molecules in contrast to the instant claim limitation " when present in a mammalian cell… binds to RNA of the retrovirus, so as to inhibit replication of the retrovirus in the cell" (instant claim 1).

The CCCH zinc finger proteins are the members of a class of CCCH family (page 133, De et al. (1999) *Gene*, 228, 133-145). The "ZAP" represents a genus comprising species which are any proteins/peptides containing at least 4 CCCH zinc motifs. Although the specification discloses the protein of SEQ ID NO:1 (page 13), this cannot adequately represent the genus "ZAP" protein. The specification fails to provide examples or drawings to disclose the core or common sequence(s)/motif(s) critical for antiviral activity such as inhibiting replication of the

retrovirus in the cell. The specification failed to describe correlation between the structure and the function (the activity thereof).

The relative art teaches that a N-terminal truncation of a "CCCH-type tandem zinc-finger protein Zfp3612 results in loss-of-function (see abstract, and page 4891, left col. 2nd paragraph, Ramos et al. (2004) *Development*, 131, 4883-4893). This suggests that in addition to the zinc finger motifs, other sequence(s)/domain(s) may be important for and contribute to ZAP protein functions, and that variants of ZAP are biologically inactive including incapable of interacting with the RNAs such as viral mRNAs.

The court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] name chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". UC California v. Eli Lilly (43 USPQ2d 1398). For claims drawn to genus, MPEP section 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Also, MPEP section 2163 states that a representative number of species mean that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Instant specification fails to describe

the invention in such a way that one of ordinary skill in the art would recognize that applicants were in possession of the claimed protein at the time the application was filed.

Sufficient relevant identifying characteristics

A sufficient/representative number of species of the "genus" is not disclosed. Neither the specification nor the art in the relative field describes/teaches the fragment of/and variant ZAP polypeptide comprising at least 4 CCCH-zinc finger motifs. In the absence of direction and/or description of correlation between structure (core domain or consensus sequence) and function (e.g., inhibiting growth of RNA virus), applicants are not in possession of the claims.

Predictability in the art

The relative art (De et al.) teaches that the ZAP molecule such as 4 CCCH-zinc finger protein XC3H-1 (see abstract) is acidic protein (suggesting incapability of binding to nucleic acids) and contains no notable hydrophobic domain; and thus, its function remains unknown (page 139, left col., last paragraph, line 1 to right col., lines 3). This suggests that the level of unpredictability on the art is high.

Level of skill and knowledge in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to species which are representative of the genus discussed above. In the absence of the representative species for the full scope of the genus claimed, adequate written description requires more than a mere statement that it is part of the invention. Without a correlation between structure and function, the claims do little more than define the claimed invention by function. See *Eli Lilly*, 119, F.3d at 1568, 43USPQ2d at 1406. In this case, applicants do not describe the invention of claims 1-4, 6, and 7 as to structure of the

"variant"/"fragment" and the function such as inhibiting RNA viral growth adequately to show they has possession of the disclosed "genus" in the claimed product.

[2] *Scope enablement*

Claims 1, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because while the specification may enable the ZAP protein of amino acid sequence of SEQ ID NO:1, does not reasonably provide enablement for any ZAP variants comprising the at least 4 zinc finger motifs wherein variants refer to any structural alteration occurring outside of the motifs in reference to SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

(1) The scope of the claims/(2)The nature of the invention:

The amended claim 1 and dependent claims 6, and 7 as written are directed to an isolated mammalian zinc-finger antiviral protein (ZAP) comprising 4 CCCH type zinc finger motifs. The claim ZAP is a genus encompassing the protein variants having said motifs but having structural alteration such as mutations compared to instant SEQ ID NO:1 ZAP. The specification sets forth

that the ZAP may bind to specific cellular RNAs and stabilize thereof (page 28, lines 19-23) and specific for the virus such as Nile virus (page 15, lines 16-123). Contrary to this, the art (US 20020035246 A1) teaches that CCCH zinc finger protein SMAD binds single or double stranded DNA (claim 22), suggesting not all the CCCH-type zinc finger proteins specifically bind RNAs only. Neither the specification nor the relative art teaches what structure renders the "specificity" thereof and provides factual indicia regarding the CCCH zinc finger motifs and/or the sequence(s) outside the motifs responsible for said specific viral binding function. The relative art (US 20020035246) teaches that the CCCH-zinc finger proteins such as 'SMAD interacting protein" (see [0039]) has an RNase activity (see [0043]) which degrade RNA molecules in contrast to the instant claim limitation " when present in a mammalian cell… binds to RNA of the retrovirus, so as to inhibit replication of the retrovirus in the cell" (instant claim 1).

The relative art teaches that a N-terminal truncation of a "CCCH-type tandem zinc-finger protein Zfp3612 results in loss-of-function (see abstract, and page 4891, left col. 2nd paragraph, Ramos et al. (2004) *Development*, 131, 4883-4893). This suggests that apart from the zinc finger motifs, certain sequence(s)/domain(s) may be important for and contribute to ZAP protein functions including activity of binding RNAs, and that variants of ZAP are biologically inactive including incapable of interacting with the RNAs such as viral mRNAs. Thus, experimentation needed is not routine. In the absence of teaching and guidance as to the critical domain(s)/consensus sequence(s) necessary for the disclosed function, screening and characterizing the variant proteins/peptides containing the at least four zinc finger motifs which have the specific retrovirus binding capability or/and specific binding to the retroviral RNAs thereby inhibiting replication thereof would be beyond the realm of routine experimentation.

Therefore, the scope of the claims is outside the bounds of the enablement provided by the specification and prior art, and would have resulted in the necessity of undue experimentation.

(3) The unpredictability of the art:

The relative art (De et al.) teaches that the ZAP molecule such as 4 CCCH-zinc finger protein XC3H-1 (see abstract) is acidic protein (suggesting incapability of binding to nucleic acids) and contains no notable hydrophobic domain; and thus, its function remains unknown (page 139, left col., last paragraph, line 1 to right col., lines 3). This suggest that the level of unpredictability on the art is high.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Because the art does not teach or provide guidance as to how to make and use each members embraced in the "genus" claimed. The relative art (Barabino et al. (1997) *Gene Dev.* 11, 17031716) teaches that the role of the CCCH motif (cysteine-rich) is unknown, though its presence in the protein that interacts with nucleic acid such as involvement in RNA binding has been contemplated (page 1707, left col., lines 8-10). This suggests that the proteins/peptides as whole but not the CCCH motifs alone must be assayed for the specific retrovirus binding and inhibition of retroviral replication. The specification needs to provide sufficient guidance to be considered enabling for the claimed genus.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the structure and function correlation discussed above, unpredictability of the art, the lack of sufficient guidance in the specification

and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation to finding out bioactive variants of proteins/peptides comprising the four or more than four CCCH zinc motifs is extensively large.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of polypeptide and broad scope of disorders encompassed by the claims. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a protein chemist with several years of experience in virology as well as knowledge in protein-DNA/RAN binding. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Thus, the amount and level of experimentation needed is undue.

***Claim Rejections - 35 USC §102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

CLAIM INTERPRETATION: Claim 1 as written is broadly directed to a "ZAP" protein comprising at least 4 CCCH-zinc finger motifs (can be more than 4 CCCH due to the open-ended language "comprise" in item (a)..

Since the claims do not set forth structure for disclosed "ZAP" protein apart from the CCCH-zinc finger motifs, the art teaching said motifs would anticipate item (b) of claim 1 which is directed to activity of the ZAP protein. MPEP state that where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established; and thus, when the structure recited in the prior art is substantially identically to that of the claims, claimed properties of function are considered to be inherent (see 2112.01 (I)). Also, MPEP state that "Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658(Fed. Cir. 1990)" (see 2112.01 (II)). Thus, in the absence of disclosure of the structural indicia relative to inhibiting retroviral replication set forth in item (a) of claim 1, the prior art which teaches the structural limitation in item (a) of claim 1 would also anticipate item (b) because it refer to inherent property/function of the ZAP protein and refers to intended use thereof. Therefore, the following 102 rejections are applicable.

[1] Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by De et al. (Gene (1999) 228, 133-145).

De et al teach an isolated ZAP protein "XC3H-1 comprising 4 CCCH-zinc finger motifs and having a role in mRNA stability in vivo (see abstract and page 134, right col., lines 19-21 and lines 22-26). This teaches claim 1.

[2] Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Barabino et al. (*Gene Dev.* (1997) 11, 17031716).

Barabino et al. an isolated protein "CPSH" comprising more than four CCCH-zinc finger motifs and having RNA-binding capability (see abstract and page 1704, left col., 2nd paragraph). This teaches claim 1.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pro. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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March 29, 210